

The Examiner has made the assertion that "Applicant essentially admits that the [Medarex] reference teaches the claimed invention because an Fc- γ binding partner would also be an FcRn binding partner if said binding partner comprises an IgG." Applicants respectfully disagree with the Examiner's position, for the following reasons.

For a reference to be anticipatory, it must disclose each and every element of the claim. It also must not be accidental that the teaching of the § 102 reference discloses the claimed invention.

What Applicants pointed out in the response filed February 1, 2001, is that if Medarex were to disclose the elements of Applicants' conjugate, it would only be by accident. There are numerous possibilities in Medarex. None but one could possibly be the conjugate claimed herein. The Examiner correctly identifies that possibility, a conjugate of whole IgG and antigen. However, because it is not stated where the antigen is conjugated to the whole IgG, there is no teaching that the FcRn binding portion of Fc must be preserved. Thus, it is only by accident that one practicing the invention of Medarex would achieve a conjugate as claimed in the instant application. As such, Medarex is not an anticipatory reference.

B. Formulation

Within the rejection of claims 25-31 and 33-34 as being anticipated by Medarex, the Examiner indicated that these claims are rejected because the specific formulations add no patentable weight. In support of his argument, the Examiner cites U.S. Patent No. 6,187,757 and U. S. Patent No. 5,948,892. Applicant respectfully requests the Examiner to withdraw the rejection because the cited references are irrelevant to the instant invention and they simply do not anticipate the claims. U.S. Patent No. 6,187,757 is directed to methods and compositions involving analogs of the small molecule rapamycin (molecular weight ca. 914; "rapalogs"). The claims of the instant invention make no connection with analogs of rapamycin. Thus the Examiner has not made a *prima facie* case for rejection under 35 U.S.C. § 102 (b) over U.S. Patent No. 6,187,757. U.S. Patent No. 5,948,892 is directed to analogs of macrophage stimulating protein (MSP), and it discloses a MSP-Fc fusion protein. The claims of the instant invention make no connection with MSP and therefore neither has the Examiner made a *prima facie* rejection under 35 U.S.C. § 102 (b) over U.S. Patent No. 5,948,892. U.S. Patents 6,187,757 and 5,948,892 in no way anticipate the claims of the instant invention. Accordingly,

Applicants respectfully request the Examiner to withdraw his rejection of claims 25-31 and 33-34.

In addition, the Examiner has improperly failed to give any patentable weight to the claim limitations of the formulations and the dependent claim limitations. Medarex does not show aerosol formulation. There is no reason to deliver a composition of Medarex by aerosol. Thus, the Examiner has not made a *prima facie* case that an aerosol is the same as the “physiologically acceptable solution” of Medarex (page 9, line 9). The Examiner need only look to Remington's Pharmaceutical Sciences to appreciate that “physiologically acceptable solution,” aerosol, nasal formulation, and oral formulation are not interchangeable. Therefore, the Examiner has the burden of finding these formulation limitations in the prior art. As mentioned above, the cited U.S. Patents 6,187,757 and 5,948,892 do not meet this burden. Therefore, the Examiner has not made a *prima facie* case for rejection under 35 U.S.C. § 102 (b).

In contrast to Medarex, the instant invention provides a reason for aerosol, nasal, or oral formulation, viz., the unexpected finding that inclusion of an FcRn binding partner is central to transepithelial transport. Applicants respectfully submit that the Examiner has not given due weight to this unexpected finding.

Furthermore, the dependent claims implicitly and explicitly set forth specific components of oral, aerosol, and nasal formulations. These include, for example, the limitations of elixir, syrup, and propellant. The Examiner is referred to Section 5.5.2 (pages 45-49) of the specification and again to Remington's Pharmaceutical Sciences to appreciate that components recognized in the art make for differences among these formulations. In each instance, the formulation is selected to enhance delivery of agents across the appropriate oral/gastrointestinal, pulmonary, or intranasal epithelial barrier. As above, the Examiner has the burden of finding these formulation limitations in the prior art. Also as mentioned above, the cited U.S. Patents 6,187,757 and 5,948,892 do not meet this burden. Therefore, the Examiner has not made a *prima facie* case for rejection under 35 U.S.C. § 102 (b).

The Examiner has failed to make a *prima facie* case for rejection of claims 25-31 and 33-34 under 35 U.S.C. § 102 (b). Applicants therefore respectfully request the Examiner to reconsider and to withdraw his rejection of claims 25-31 and 33-34 under 35 U.S.C. § 102 (b).

C. “Specific for” language of Medarex

The Examiner's remarks indicate that the 102(b) rejection rests on the "specific teaching" of WO 92/05793 ("Medarex") that "an antigen can be coupled to an antibody, or fragment thereof, specific for an Fc receptor of an antigen presenting cell" [emphasis supplied by Examiner]. Applicants respectfully submit to the Examiner that Medarex does not anticipate the instant invention because of the special significance of the words "specific for" as used in the quoted passage from Medarex. As used in the art, an antibody or fragment thereof specific for a target refers to a whole antibody or a fragment thereof that necessarily includes an antigen binding site. The antigen binding site resides in that part of an antibody that confers binding specificity for the particular antigen against which that antibody has been raised. As used in the art, the antigen binding site is or most often corresponds to part of one of the following fragments of a whole antibody: Fv, Fab, Fab', or F(ab')₂. These fragments of an antibody are physically and functionally distinct from the Fc fragment. In particular, the Fc fragment is not involved in the antigen-specific antibody-antigen interaction that characterizes a particular antibody.

Medarex makes the meaning of "specific for" clear. Beginning at page 5, line 30, following a discussion of how to make and characterize monoclonal antibodies that bind to an epitope of Fc γ RI which is distinct from the Fc binding site of the receptor, Medarex teaches:

Bispecific antibodies are single, divalent antibodies which have two different antigen binding sites (variable regions). In the bispecific antibodies of this invention, one of the antigen binding sites is specific for the receptor of the antigen-presenting cell and has the characteristics set forth above, and the other binding site is specific for the antigen to be targeted to the antigen-presenting cell. [emphasis added]

Medarex goes on to teach at page 6, beginning at line 10:

Heteroantibodies are two or more antibodies or antibody-binding fragments (Fv, Fab, Fab', or F(ab')₂) of different binding specificity linked together. Heteroantibodies comprise an antibody (or antigen-binding fragment) specific for the receptor of the antigen-presenting cell, coupled to an antibody (or antigen binding fragment) specific for the antigen to be targeted. [emphasis added]

Taken in context, it is clear that Medarex uses "specific for" to refer to binding specificity provided by an antigen binding site or, equivalently, antigen binding fragment of an antibody.

Medarex places on equal footing (1) binding specificity for an antigen to be targeted and (2) binding specificity for the receptor of the antigen-presenting cell. As is well known in the art and as taught by Medarex, such binding specificity is derived from the active immunization of an animal with (1) the antigen to be targeted or (2) the receptor of the antigen-presenting cell, followed by selection for antibodies having high affinity for the respective immunogen. To interpret Medarex otherwise would obviate the entire teaching therein that relates to bispecific antibodies.

According to the teachings of Medarex, the specificity for the interaction between the bispecific reagent of Medarex and the receptor of the antigen-presenting cell is furnished by the binding specificity of the bispecific reagent for the receptor of the antigen-presenting cell. This is so because Medarex clearly teaches that bispecific agents without specificity for the receptor of the antigen-presenting cell will be substantially blocked by the natural ligand for the receptor. According to Medarex, binding of nonspecific antibodies (having Fc) will be substantially blocked by circulating antibodies (also having Fc).

Thus "an antibody, or fragment thereof, specific for an Fc receptor of an antigen presenting cell", as used in Medarex, necessarily includes an antigen binding site that has a binding specificity for an Fc receptor of an antigen presenting cell.

This is to be distinguished from the instant invention, which does not require an antigen binding site that has a binding specificity for an Fc receptor of an antigen presenting cell. The instant invention relies instead on a functional domain (FcRn binding partner) capable of binding to FcRn. Among other agents that fulfill this requirement are, for example, Fc fragments and antigen-nonspecific IgG. Such FcRn binding partners unquestionably do not, in contrast to Medarex, require an antigen binding site that has a binding specificity for an Fc receptor of an antigen presenting cell.

2. Rejection of claims 25-34 under 35 U.S.C. § 112, first paragraph

The Examiner has indicated that claims 25-34 are rejected under 35 U.S.C. § 112, first paragraph, for insufficient written description. It is requested that the Examiner withdraw his rejection in view of the following remarks.

In making the rejection, the Examiner has cited Regents of the University of California v. Eli Lilly and Co., 119 F.2d 1559 (CAFC, 1997) for the proposition that the specification fails to

disclose a representative number of species to describe the claimed genus (FcRn binding partners). The Lilly case dealt specifically with a genus of cDNAs. The holding in that case was that “a description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.” Lilly 119 F.2d at 1569.

In contrast to the holding of Lilly, the written description guidelines for antibodies specifically endorses a claim drawn to a genus described by an isolated antibody capable of binding to a defined antigen. With respect to a genus of antibodies so claimed, the particular structures of the antibodies need not be specified under the standard of Lilly. In fact, in direct contrast to the holding of Lilly, the function of the antibody – specific binding to a known antigen – and not the structure of the antibody, provides sufficient description.

In the instant application, the claim element at issue is an FcRn binding partner. While the Applicants do not mean to limit “FcRn binding partner” to mean “antibody”, it should be clear that what is at issue is more apposite to the situation of what is required of a claim to a genus of antibodies than to the situation of what is required of a claim to a genus of cDNAs. That said, the specification nevertheless clearly lays out certain structural elements of Fc fragments that may participate in FcRn binding, namely, the Fc-FcRn contact residues 248, 250-257, 272, 285, 288, 290-291, 308-311, 314, 385-387, 428, and 433-436. Page 14, lines 13-15. Furthermore, in view of the well-developed and mature technology of making antibodies, antibody fragments, and antibody derivatives, the spectrum of FcRn binding partners is fairly disclosed by the written description.

In view of the foregoing remarks, Applicants respectfully submit that, contrary to the Examiner’s position, the specification provides sufficient written description for “FcRn binding partner”. Applicants therefore respectfully request the Examiner to withdraw the rejection of claims 25-34 under 35 U.S.C. § 112, first paragraph.

3. Rejection of claims 25-34 under 35 U.S.C. § 103 over U.S. Patent 5,428,130 in view of WO 92/05793

The Examiner has indicated that claims 25-34 have been rejected under 35 U.S.C. § 103 over U.S. Patent 5,428,130 (“the ’130 patent”) in view of WO 92/05793 (“Medarex”). The

rejection appears further to rely somehow on Canadian Patent application 2,045,869 ("the '869 application"). It is requested that the Examiner withdraw this rejection in view of the following remarks.

With respect to Medarex it should be pointed out that the Examiner has mischaracterized what that reference actually teaches. If Medarex does not teach what the Examiner asserts that it teaches, then the Examiner has not made a *prima facie* case for the rejection.

The Examiner states that Medarex teaches a pharmaceutical preparation for activating an immune response comprising a conjugate of a hepadnaviridae (hepatitis) antigen, *an Fc binding fragment of IgG*, and a *pharmaceutically acceptable carrier including saline*. The Examiner's characterization of the teachings of Medarex is incorrect in at least the following two ways. First, in contrast to the Examiner's assertion of what Medarex teaches, Medarex makes no teaching about an Fc binding fragment of IgG. It is not clear what the Examiner means by "an Fc binding fragment of IgG". Medarex teaches the use of fragments of IgG that bind to Fc receptor with higher affinity than do Fc fragments themselves. In other words, Medarex teaches the use of antigen-specific binding portions of IgG, which, as those of skill in the art understand, may include Fab fragments and the like, but not Fc fragments themselves. Medarex specifically points out that it is binding by the Fc fragment that poses the problem to be overcome by the patent. Medarex at page 2, lines 4-8. Second, also in contrast to the Examiner's assertion of what Medarex teaches, Medarex makes no teaching about a pharmaceutically acceptable carrier including saline. The cited passage at page 9, line 5 is taken out of context. That passage refers to the method for preparing a preformed immunochemical complex by incubating an antigen with a bispecific binding reagent in saline at 37°C. The method teaches saline as a medium suitable for preparing a preformed immunochemical complex, and it does not teach saline as a pharmaceutically acceptable carrier.

Since Medarex clearly does not teach what the Examiner asserts that it teaches, the Examiner has not made a *prima facie* case for the rejection in view of Medarex. Accordingly, Applicants request the Examiner to withdraw his rejection of claims 25-34 under 35 U.S.C. § 103 over U.S. Patent 5,428,130 in view of WO 92/05793.

The Examiner somehow relies on the '869 application in making the rejection. It is not clear how the Examiner intends to use the '869 application. The Examiner appears to suggest that the '869 application teaches the use of hepatitis as the ligand of interest. Alternatively, the

Examiner may be suggesting that the '869 application, in place of the '130 patent, can be combined with Medarex. The '869 application teaches fusion proteins having a human protein or portion thereof, not belonging to the immunoglobulin family, and portions of constant heavy or constant light chains of immunoglobulins of various subclasses (IgG, IgM, IgA, IgE). The '869 application makes no teaching as to the use of hepatitis as the ligand of interest. Neither does the '869 application provide any teaching with regard to pharmaceutical preparations or routes of administration.

For the reasons provided above with respect to Medarex, combining the '869 application with Medarex would not make a prima facie case for a rejection under 35 U.S.C. § 103. Similarly, combining the '869 application with the '130 patent, either on its own or in further combination with Medarex, also does not make a prima facie case for a rejection under 35 U.S.C. § 103. Therefore Applicants request the Examiner to reconsider and to withdraw his rejection of claims 25-34 under 35 U.S.C. § 103.

Applicants believe that the application is in condition for allowance. A Notice of Allowance is earnestly solicited.

Respectfully submitted,



Alan W. Steele, Reg. No. 45,128
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, MA 02210
Tel. (617) 720-3500

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